REMARKS/ARGUMENTS

Claims 1-35 are pending in the present application. Claims 3, 5-7, 9-10, 12-15, 18-35 have been withdrawn from consideration as directed to a non-elected invention. Claims 1, 2, 4, 8, 11, 16 and 17 are the subject of this Office Action. By virtue of this response, claims 1 and 11 have been cancelled; claims 2, 4, and 8 have been amended; and claims 36 and 37 have been added. Accordingly, claims 2, 4, 8, 16, 17, 36, and 37 are currently under consideration.

Claims 2 and 4 have been amended to recite a fusion protein comprising human alpha 1-antitrypsin or a functionally active portion thereof and human secretory leukocyte protease inhibitor or a functionally active portion thereof. The dependency of claim 8 has been amended in view of cancelled claim 1. New claims 36 and 37, to a fusion protein of human AAT and human SLPI, comprising SEQ ID NOS: 8 and 16, respectively, have been added (Applicants note that these sequences have been deemed allowable by the Examiner, see Office Action, p. 9). Support for claims 2, 4, 36 and 37 may be found in the specification as filed at, e.g., ¶¶59 and 67 and SEQ ID NO: 2 (human AAT); ¶ 68 and SEQ ID NO: 4 (human SLPI); ¶69 and SEQ ID NOS: 8 and 16, and Examples 1, 3, and 5 (fusion proteins of human AAT and SLPI); and ¶¶ 62 and 63 (functionally active portions thereof).

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

In view of the preceding amendments and the remarks that follow, reconsideration and withdrawal of the outstanding objections and rejections is respectfully requested.

Request for rejoinder

Applicants reiterate their request for rejoinder of presently excluded method claims 26-35, to the extent that they incorporate all the limitations of the composition claims. The Office has indicated that once allowable composition claims are identified, then method claims which incorporate all the limitations of the composition claims may be rejoined (paper no. 12, page 2).

Withdrawal of previous objection and rejection

Applicants acknowledge with appreciation the withdrawal of the objection under 37 CFR §1.75(c) (Office Action, page 2) and the rejection under 35 U.S.C. §112, first paragraph, for alleged lack of enablement (Office Action, page 9).

Examiner Interview of July 2, 2003

Prior to addressing the issues set forth in the outstanding Office Action, Applicants' representatives would like to thank Examiner Walicka and Supervisor Hudson for the courtesy extended to them during the July 2, 2003 telephonic interview. This interview was helpful in providing the response set forth herein. In particular, Applicants' representatives thank Examiner Walicka and Supervisor Hudson for suggestions regarding amendments to more clearly delineate claimed subject matter that is adequately described in the specification, and for suggestions concerning areas of the specification to be more clearly brought to the attention of the Office in regard to written description of the claims. The present claims and the following Remarks reflect these suggestions.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 8 and 11 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As a preliminary matter, without conceding the correctness of the Examiner's position and merely to place the claims in condition for allowance, Applicants have cancelled claims 1 and 11 and amended claim 2 to recite a fusion protein comprising human alpha 1-antitrypsin (AAT) or a

functionally active portion thereof and human secretory leukocyte protease inhibitor (SLPI) or a functionally active portion thereof, where the fusion protein has protease inhibitor activity.

The following remarks pertain to the rejection of pending claims and, as pertinent, to the claims as amended.

Applicants submit that the claimed invention was described in the application as filed, by demonstration of reduction to practice and by disclosure of numerous identifying characteristics of the fusion proteins as presently claimed. Applicants respectfully remind the Examiner that there is a "strong presumption that an adequate written description of the claimed invention is present when the application is filed" (MPEP §2163.I.A). Furthermore, as discussed in the interview, narrowing the scope of the claims to specify human AAT and SLPI as components of the claimed fusion proteins further reduces the extent of written description requirement correspondingly. In the instant specification, Applicants have described not only actual reduction to practice of fusion proteins comprising human AAT and human SLPI, but representative sequences of both human AAT and human SLPI that may be used in the invention, and further descriptive characteristics discussed below; in addition, the claims themselves recite structural and functional characteristics of the fusion proteins, which are sufficient identifying characteristics.

The MPEP states, "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice . . . or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus." MPEP §2162.II.A.3.(a)(ii) [emphasis added] Thus, reduction to practice alone, or disclosure of relevant identifying characteristics alone, is sufficient to satisfy the written description requirement. Applicants provide both 1) a description of actual reduction to practice of two working embodiments of fusion proteins comprising human AAT and human SLPI, and 2) detailed disclosure of relevant structural and functional identifying characteristics of AAT and SLPI and their relationships, including in the claims themselves. Either of these alone would be sufficient to satisfy the written description requirement of 35 U.S.C. §112, ¶1; together they are more than sufficient to satisfy the requirement. This is especially true because the level of knowledge and skill in the art at the time the application was filed was high. "Generally,

there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification." MPEP §2163.II.A.2.

1) Reduction to practice: As discussed during the interview, Applicants have demonstrated reduction to practice of two embodiments of a fusion protein of human AAT and human SLPI--SLAPI and r-SLAPI--and the Examiner has conceded "[T]he claims contain allowable subject matter. Applicants are the first to produce bifunctional fusion protease inhibitors that are set forth by SEQ ID NO: 8 [SLAPI] and 16 [r-SLAPI]." Office Action, page 9. This reduction to practice includes detailed descriptions of the construction of the fusion protein genes (Examples 1 and 3), expression in yeast (Example 5), and assay for protease inhibitor activity of fusion proteins expressed in various culture systems (Example 5).

The courts have stated that reduction to practice is a strong indicator of adequate written description; in fact, it is arguably sufficient in itself as written description: "It is true that reduction to practice ordinarily provides the best evidence that an invention is complete . . . reduction to practice is sufficient evidence of completion . . ." *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 66 (1998) (quoted in MPEP in reference to written description requirement at § 2163.II.A.3.(a).). In the case of a claim to a genus, the question is whether a representative number of species has been described. "What constitutes a 'representative number' is an inverse function of the skill and knowledge in the art." MPEP §2162.II.A.3.(a)(ii).

The study of protease inhibitors, especially alpha-one antitrypsin and secretory leukocyte protease inhibitors, the components of the present invention, was at a level of sophistication at the time the application was filed that one of skill in the art would instantly recognize that the Applicants had possession of the invention at the time the instant application was filed from the actual reduction of practice of two embodiments. The structure of both AAT and SLPI were well-known and their function was likewise well-characterized; i.e., the components of the fusion proteins were not unknown structures but rather structures that one of skill in the art would recognize and comprehend. Given the level of knowledge and skill in the art, reduction to practice of two species, where the protein components were joined in both the forward (SLAPI) and reverse (r-SLAPI) orientations would have indicated to one of skill in the art that the Applicants were in

possession of the genus at the time of application. "There may be situations where one species adequately supports a genus." MPEP §2162.II.A.3.(a)(ii). Here, there are two species that have been reduced to practice, in a sophisticated and highly skilled field. This alone would provide adequate written description so that one of skill in the art would recognize that the inventors possessed the invention, even in the absence of the additional disclosure described below.

2) Description of relevant identifying characteristics: The characteristics of the claimed fusion proteins, as well as their relationship, are described in the specification in sufficient detail to indicate that the Applicants possessed the invention (and are recited in the claims). Each component of the fusion proteins is well-known in the art and is described in the specification.

The claims themselves recite the structure and function of the claimed fusion proteins. Claim 2 recites a fusion protein comprising human AAT or a functionally active portion thereof and human SLPI or a functionally active portion thereof that has protease inhibitor activity. Human (and other) AAT is a specific structure or set of structures, well-known to those of skill in the art. The same is true for human (and other) SLPI. Likewise, protease inhibitor activity is a known function in the art. Thus, the claims themselves recite the structure and function of the fusion proteins in a manner that demonstrates to one of skill in the art that the inventors had possession of the claimed invention.

In addition, as discussed in the interview, the sequences for human AAT and human SLPI, as well as their allelic forms and recombinant forms, are not only well-known to those of skill in the art, they are also described in the specification. The specification not only provides a sequence for human AAT (SEQ ID NO: 2), but provides allelic sequences of human AAT (see, e.g., Carrell et al., *Nature* 298: 329-334, 1982, referenced in ¶67 of the instant application) as well as recombinant sequences containing amino acid substitutions (see, e.g., U.S. Patent No. 4,732,973, referenced in ¶67 of the instant application). Similarly, for SLPI, the native human sequence is specifically given in SEQ ID NO: 4, and other active sequences are provided (see, e.g., U.S. Patent Nos. 4,760,130; 5,464,822; 4,845,076; 5,633,227; 5,851,983; 5,871, 956; 5,900,400; 6,017,880; and 6,291,662, referenced in ¶68 of the instant application). Thus, in addition to structures of AAT and SLPI being well-known in the art, the application as filed describes numerous specific sequences of AAT and SLPI, including human AAT and SLPI, that are components of the fusion proteins of the invention.

Thus, sequences of both components of the claimed fusion proteins are known in the art and the specification refers to and describes these components. As noted above, "Information which is well known in the art need not be described in detail in the specification." MPEP §2163.II.A.2. The claimed invention is clearly conveyed to one skilled in the art and thus the written description requirement is satisfied.

The claims recite that the fusion proteins may contain "functionally active portions" of AAT and/or SLPI. This is also fully described in the specification, both in terms of specific functionally active portions, and in terms of defining what is meant by a "functionally active portion." The specification states that "Functionally active portions of AAT may also be used in the present invention, for example, those described in U.S. Pat. Nos. 6,068,994 and 4,732,973, and in A. Hercz, Proteolytic cleavages in alpha-one antitrypsin and microheterogeneity, *Biochem. Biophys. Res. Comm.* 128: 199-203, 1985" (specification, ¶67) and "[F]unctionally active portions of SLPI (see, *e.g.*, U.S. Patent Nos. 4,760,130; 5,464,822; 4,845,076; 5,633,227; 5,851,983; 5,871, 956; 5,900,400; 6,017,880; and 6,291,662), . . .may be used in the invention." Specification, ¶68. Thus, functionally active portions of both human AAT and human SLPI were well-known to one of ordinary skill in the art and are fully described by reference in the application.

The linkage of the protease inhibitors into fusion proteins is also described in detail in the specification, see, e.g., ¶69, including the two orientations used in the working examples, as well as possible additional amino acids that may be inserted between the protease inhibitors.

In addition to reciting the structural components of the fusion proteins (AAT and SLPI), the claims further recite that the fusion proteins have "protease inhibitor activity," a functional limitation. Protease inhibitor function was well-known in the art. The specification describes assay of embodiments of the invention for protease inhibitor activity, including inhibition of the major proteases inhibited by AAT and SLPI (elastase and tryptase, respectively), in Examples 5 and 9. Further assays for elastase inhibitor activity are fully described in Examples 6 and 8.

Thus, the claims themselves recite the structure and function of the claimed fusion proteins, and the specification further describes structural and functional characteristics of the claimed proteins in detail. This, in itself, is sufficient to satisfy the written description requirement. In combination with the reduction to practice of the invention, there is more than sufficient information

in the application as filed so that one of ordinary skill in the art would have recognized that Applicants possessed the claimed invention.

Response to Examiner's comments: While not conceding the correctness of the Examiner's position, and maintaining the arguments made in their Response mailed March 3, 2003 (paper 15), Applicants note that the Examiner's comments regarding claims 1 and 11 are rendered moot by the cancellation of these claims. Regarding claim 2, the Examiner has made several comments which are addressed here.

The Examiner has stated that "Human ATT [sic] has more than 50 natural allelic forms, and the scope of the claim comprises any ATT including recombinant forms. Also, SLPI is a generic protein and the genus comprises any variant of human and animal SLPI variant." Office Action, page 7. Applicants first refer the Examiner to the discussion above, which addresses these concerns. Applicants further note that the claims as amended recite human AAT and human SLPI, reducing the number of possible forms significantly. Furthermore, the specification describes numerous forms of AAT and SLPI that are suitable for use in the invention. In addition, an exhaustive listing of every allelic form of the component proteins need not be given, for both proteins and their allelic forms were well-known in the art at the time of filing, and one of skill in the art would have recognized that the Applicants had possession of the claimed invention without every possible combination being described explicitly in the specification, thus satisfying the written description requirement. "Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification." MPEP 2163.II.A.2.

The Examiner has stated that "Combination of any two inhibitors, or their functional parts, does not necessary lead to a fusion protein having the desired function specificities of both components . . . . one skilled in the art realizes that the change of one amino acid of a protein my [sic, "may"] lead to its inactivation. Therefore, not any combination of ATT [sic, "AAT"] and SLPI will result in a fusion protein having both functions. Thus, providing extensive disclosure of the component inhibitors . . . is not a substitute for disclosure of a genus of bifunctional inhibitors claimed in claim 2." Office Action, page 7. Applicants respectfully submit that, as discussed above,

the invention has been adequately described. Further, an assay for determining the claimed activity is known in the art and is described in the specification. As stated by the courts, and acknowledged by the Office, every species within a claimed genus need not be iterated.

"There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." MPEP §2163.I.A. Applicants respectfully submit that the Examiner has not rebutted this presumption, especially in view of actual working examples of the claimed fusion proteins, coupled with description provided in the specification, coupled with knowledge in the art. As noted above, not one but two operative reductions to practice are described in the present application, thus, clearly, the Applicants have shown that combinations of the inhibitors as claimed does result in a functional fusion protein, including combinations in varying orientations of the component proteins. Furthermore, the Applicants are not claiming inactive proteins; indeed, the claims specify that the fusion protein has the function of "protease inhibitor activity," and the fact that a single amino acid change can render a protein inactive is not relevant to written description of the claimed invention. Thus, the Office has not met its burden to establish lack of written description.

The Examiner has further stated that "The specification fails provide the identifying structural characteristics of said genus." Office Action, page 7.

First, Applicants respectfully submit that this is not the requirement for a written description of the claimed invention under 35 U.S.C. §112, first paragraph. The MPEP states that "Possession may be shown in many ways. For example, possession may be shown by describing *an actual reduction to practice* of the claimed invention . . . [or] *any description of sufficient, relevant, identifying characteristics* so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." MPEP §2163.II.A.3.(a) [emphasis added].

Second, the specification and, indeed, the claims themselves provide more than sufficient structural identifying characteristics of the genus. The claims recite that the fusion protein contains both human AAT, or functionally active portion thereof, and human SLPI, or functionally active portion thereof. These are unambiguous, well-known structural identifying characteristics of the claimed genus. Further, in the instant specification, Applicants have described not only actual reduction to practice, but representative sequences of both AAT and SLPI that may be used in the invention, and further descriptive characteristics given above. Applicants respectfully submit that

this is sufficient, relevant, identifying characteristics and that a person of skill in the art would recognize that the inventor had possession of the claimed invention.

In sum, Applicants have amply demonstrated that the invention as presently claimed was described in the application as filed, by demonstration of reduction to practice and by disclosure of identifying characteristics of the fusion proteins as presently claimed. Given the "strong presumption that an adequate written description of the claimed invention is present when the application is filed." (MPEP §2163.I.A), Applicants submit that the claims are adequately described in accordance with 35 U.S.C. §112, ¶1, and respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 4, 8, 16 and 17 stand rejected under 35 U.S.C. 112, second paragraph as allegedly indefinite. The Examiner has commented on two issues regarding indefiniteness. The first was the use of the word "about" in the claims, which the Examiner stated was "a relative term, which renders the claims indefinite." Applicants maintain and reiterate points made in their previous response, i.e., the use of a relative term is not *per se* indefinite and the use of "about" is common and accepted in the description of amino acid sequences (see communication mailed March 3, 2003, paper 15, for complete response).

The second issue concerned whether "the polypeptide consisting of [sic, "comprising"] amino acids 1-394 or 1-107 remains indefinite as long as it is not identified by its sequence number . . ." (Office Action, page 3). Without conceding the merit of the Examiner's argument, and while maintaining their arguments of the previous response (communication mailed March 3, 2003), Applicants note that claim 4 has been amended to recite human AAT and human SLPI, and that claim 4 as amended clearly meets the requirements of 35 U.S.C. 112, second paragraph.

"The test for definiteness under 35 U.S.C. 112, second paragraph, is whether 'those skilled in the art would understand what is claimed when the claim is read in light of the specification.'" MPEP §2173.02, citing *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F2d 1565, 1576 (Fed. Cir. 1986). Amended claim 4 would be understood by one of skill in the art when read in light of the specification. The use of the limitation "human" removes "all variants of ATT [sic AAT] from other animals" (Office Action, page 4) from the scope of the claims. The specification explicitly gives a sequence for human AAT (SEQ ID NO: 2) and for human SLPI

(SEQ ID NO: 4), and references many other sequences. The Examiner has stated that, "Amino acid 1-395 are not the same in all human allelic forms and in other all ATT, similarly amino acids 1-107 of SLPI are not the same in all human, animal, and recombinant variants." Office Action, page 4. As noted, non-human forms of the proteins are now not included in the claims. As for human allelic forms, for AAT these forms are well-known—the Examiner herself notes that "the IDS teaches that there are more than 50 allelic forms." Office Action, page 4. These forms can only be taught if they are known in sufficient detail to be identified by one of skill in the art, and the fact that there are more than 50 is not germane to whether the claims are definite. "Breadth is not indefiniteness." MPEP §2173.04. As noted, many sequences for AAT and functionally active portions thereof are given by reference in the application (see, e.g., Carrell et al., *Nature* 298: 329-334, 1982, Hercz, *Biochem. Biophys. Res. Comm.* 128: 199-203, 1985, and U.S. Patent Nos. 4,732,973, 6,068,994, specification, ¶67), and for any not specified in the specification, one of skill in the art need only consult the literature or public databases to determine whether a particular sequence is a human AAT or a functionally active portion thereof.

For SLPI, the human SLPI gene appears to be a relatively nonpolymorphic, stable gene. See, e.g., Abe, T ., Kobayashi, N., Yoshimura, K., Trapnell, B.C., Kim, H., Hubbard, R.C., Brewer, M.T., Thompson, R.C. and Crystal, R.G., Expression of the secretory leukoprotease inhibitor gene in epithelial cells *J. Clin. Invest.* 87 (6), 2207-2215 (1991), a copy of which is attached for the Examiner's convenience. Thus the sequence given in the specification, together with cited patents that disclose possible amino acid substitutions (e.g., U.S. Patent Nos. 4,760,130; 5,464,822; 4,845,076; 5,633,227; 5,851,983; 5,871, 956; 5,900,400; 6,017,880; and 6,291,662) , as well as databases and the literature, allow one of skill in the art to determine whether a particular sequence is human SLPI or a functionally active portion thereof.

Applicants respectfully submit that the claimed subject matter has been described in such a way as to apprise one of skill in the art of the metes and bounds of the invention. "[The Examiner] should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness." MPEP §2173.02 [emphasis in the original]. Given the level of knowledge in the art, the explicitly described sequences and those described by reference, and the definition of terms provided by the specification, the Applicants have defined the patentable subject matter with a reasonable degree of particularity and distinctness, and respectfully request that the

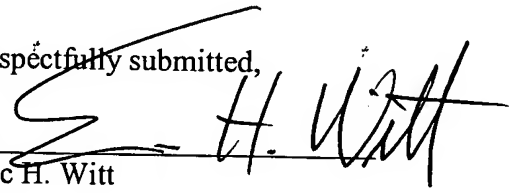
rejection be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant(s) petition(s) for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 368292000200.

Dated: September 11, 2003

Respectfully submitted,

By 

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